REMARKS

Reconsideration and withdrawal of the rejections of the claims, in view of the amendments and remarks herein, is respectfully requested. Claim 200 is amended, claim 201 is canceled and claims 233-234 are added; as a result, claims 173-194, 196-200, 202-203, 205-211, 231, and 233-234 are now pending in this application.

The 35 U.S.C. § 112, First Paragraph, Rejections

Claim 231 was rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement over the recitation of "small vessel disease". This rejection is respectfully traversed.

The Examiner acknowledges that the phrase "small vessel disease" is understood by the art (page 2 of the Office Action). Applicant need not teach what is well-known to the art. Hybritech, Inc. v. Monoclonal Antibodies, Inc., 231 U.S.P.Q. 81, 94-95 (Fed. Cir. 1986).

What is required to provide an adequate written description for a claimed genus is that the specification provides a sufficient description of a representative number of species by an actual reduction to practice, reduction to drawings or by a disclosure of relevant, identifying characteristics, i.e., by a structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics (Guidelines for Examination of Patent Applications under the 35 U.S.C. § 112(1) Written Description Requirement, Fed. Reg., 66, 1099 (2001)).

Applicant has provided a representative number of "small vessel diseases" (see page 12 of the specification) so that one of skill in the art would recognize that Applicant was in possession of the use of compounds of formula (I) to treat conditions including small vessel diseases.

Claims 200-201, 203 and 205-206 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In particular, the Examiner asserts that the instant specification does not describe or exemplify all agents which have the

property of having reduced estrogenic activity relative to tamoxifen, reduced DNA adduct formation relative to tamoxifen or any combination thereof. This rejection is respectfully traversed.

Applicant's specification discloses that agents that have reduced estrogenic activity (function) relative to tamoxifen (structure) or reduced DNA adduct formation (function) relative to tamoxifen (structure), and that are structural analogs of tamoxifen, are useful to increase active TGF-beta1 levels (function) in a mammal. Thus, Applicant was in possession of the common features possessed by members of the genus, i.e., the agents elevate active TGF-beta1 levels, have reduced estrogenic activity relative to tamoxifen or reduced DNA adduct formation relative to tamoxifen, and are structural analogs of tamoxifen.

Therefore, withdrawal of the § 112(1) "written description" rejections is respectfully requested.

The Obviousness-Type Double Patenting Rejections

Claims 173-194, 196-203, 205-211, and 231 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 153-173 of copending application Serial No. 10/729,056. As Serial No. 10/729,056 has not yet issued, a terminal disclaimer is not required.

Claims 200-201 and 205-206 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 8 of U.S. Patent No. 6,410,587. This rejection is respectfully traversed.

Claim 8 in the '587 patent is directed to a method for lowering serum cholesterol, where a compound of formula (VI) is administered. In contrast, claim 200 is directed to a method for preventing or treating a cardiovascular or vascular indication characterized by a decreased lumen diameter, wherein the agent elevates active TGF-beta1 levels, and has reduced estrogenic activity relative to tamoxifen and/or reduced DNA adduct formation relative to tamoxifen, and is a structural analog of tamoxifen.

Accordingly, withdrawal of the obviousness-type double patenting rejection over claim 8 in the '587 patent is respectfully requested.

The 35 U.S.C. § 102 Rejections

Claims 173-182, 186-193, 196-201, 203, 205-211, and 231 were rejected under 35 U.S.C. § 102(b) as being anticipated by Ito et al. (WO 94/09764), as purportedly evidenced by the abstract for Schilling Immunvaskulitis Therapiewoche, 25:1157 (1975). Claims 200 and 205-206 were rejected under 35 U.S.C. § 102(b) as being anticipated by Connolly et al. (U.S. Patent No. 5,250,561). These rejections are respectfully traversed.

Ito et al. disclose the use of toremifene to treat autoimmune diseases. In particular, it is disclosed that the administration of 100 mg/kg toremifene orally every day for 13 weeks to mice with spontaneous autoimmune disease inhibited the appearance of autoreactive T cells (page 8). Autoimmune diseases are degenerative diseases where the body's immune system destroys tissues (see page 191 of Churchill's Medical Dictionary, Churchill Livingstone, Inc., New York, NY (1989), a copy is enclosed herewith).

To constitute anticipation, all material elements of a claim must be found in one prior art source. In re Marshall, 577 F.2d 301, 198 U.S.P.Q. 344 (C.C.P.A. 1975).

Ito et al. do not teach or suggest the use of a cytostatic dose of a compound of formula (I), e.g., to treat a cardiovascular or vascular indication characterized by a decreased lumen diameter, the use of a compound of formula (I) to increase TGF-beta levels, the use of a compound of formula (I) to treat arteriosclerosis or small vessel disease, or the use of an agent that directly or indirectly elevates the level of active TGF-beta1 in a mammal, where the agent has reduced estrogenic activity relative to tamoxifen, reduced DNA adduct formation relative to tamoxifen, or any combination thereof, and is a structural analog of tamoxifen.

Connolly et al. disclose compounds that inhibit HMG CoA reductase and cholesterol biosynthesis and their use to treat or prevent hypercholesterolemia, hyperlipoproteinemia, and atherosclerosis.

Connolly et al. do not teach or suggest the use of structural analogs of tamoxifen to elevate the level of active TGF-beta1 in a mammal, where the agent has reduced estrogenic activity relative to tamoxifen, reduced DNA adduct formation relative to tamoxifen, or any combination thereof.

Therefore, withdrawal of the § 102(b) rejections is respectfully requested.

The 35 U.S.C. § 103 Rejections

Claims 173-181, 205-211 and 231 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Sawada et al. (Pharmacometrics, 44:357 1992). Claims 183-185, 194 and 202 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Ito et al., and claims 173-194 and 196-203 and 205-211 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Yang (U.S. Patent No. 5,455,941). These rejections are respectfully traversed.

To establish a *prima facie* case of obviousness, the Examiner must meet three criteria. The Examiner must establish that (1) there is some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings; (2) there is a reasonable expectation of success; and (3) the prior art reference (or references when combined) teach or suggest all the claim limitations. See M.P.E.P. §§ 706.02(j) and 2143. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on Applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

Sawada et al. disclose that in order to evaluate the safety of toremifene, which is expected to be used in the treatment of breast cancer, toremifene was administered to female rats (page 1 of the translation) for 52 weeks. In particular, it is noted that "[b]ecause the use of this drug is to be limited to female patients, only female rats were tested" (page 1 of translation). It is disclosed that the animals were divided into a control group and groups administered 0.01, 0.1, 1 and 10 mg/kg toremifene per day, and that the administered dose was 5 ml/mg. These amounts were based on earlier studies where a 0.7 mg/ml group showed toxic changes, including suppressed weight gain and total cholesterol reduction. Specifically, in concluding, Sawada et al. state that when toremifene was administered to female rats, "toxic changes were observed in the female reproductive system, pituitary, liver function and body weight" (page 12 of translation).

Thus, Sawada et al. teach that the decrease in cholesterol is part of a general toxic syndrome arising from higher than appropriate dosages of toremifene, which corresponds with suppressed weight gain and a drop in feed consumption. Sawada et al. also link decreased cholesterol to a change in liver function, which, in the case of tamoxifen, can be associated with

liver tumor formation. See Sawada et al. at page 13. Sawada et al. is therefore teaching against the use of such dosages, due to the associated toxicity. In addition, Sawada et al. fail to teach, suggest, or imply that toremifene is or could be a therapeutic anti-cholesterol agent. In particular, Sawada et al. measured total cholesterol levels in the rats, which does not distinguish between a reduction in "good" cholesterol versus "bad" cholesterol. Moreover, based upon the disclosure of Sawada et al., it is unclear whether the reduction in total cholesterol is due to the action of toremifene on TGF-beta levels, whether it is due to the toxicity of toremifene, or if it is due to the decrease in feed consumption. In addition, an abnormal estrous cycle was observed in the 0.1 mg/kg group, and uterine atrophy and the absence of an estrous cycle occurred for nearly three weeks in the 1 mg/kg group (page 9 of the translation).

The Examiner asserts that it would have been obvious to one of ordinary skill in the art to employ toremifene citrate in 0.1 mg/kg or more including 10 mg/kg to a mammal at risk or afflicted with cardiovascular or vascular indication such as atherosclerosis. One would have been motivated to employ toremifene citrate in 0.1 mg/kg or more including 10 mg/kg (cytostatic dose) to a mammal at risk or afflicted with cardiovascular or vascular indication such as atherosclerosis because Sawada et al. teach the administration of toremifene citrate in 0.1 mg/kg or more including 10 mg/kg (cytostatic dose) to female rats showed decrease in total cholesterol in rats. The Examiner continues, asserting that one would be further motivated to make such a modification in order to achieve an expected benefit of lowering total cholesterol level in a mammal suffering from atherosclerosis, and that the claimed compounds are so closely related structurally to the compounds of the references to be structurally obvious therefrom in the absence of any unobvious or unexpected properties.

While the toxicity observed with toremifene administration, including suppressed weight gain, total cholesterol reduction, and abnormalities of the uterus and estrous cycles, may be acceptable to treat cancer, Sawada et al. do not provide the suggestion or motivation to reach the present invention, e.g., the use of a compound of formula (I) to prevent or treat a mammal having or at risk of a cardiovascular or vascular indication characterized by a decreased lumen diameter or treat arteriosclerosis and small vessel disease.

Therefore, Sawada et al. teach away from the use of toremifene or analogs thereof, for instance, to treat diseases other than cancer.

With respect to Ito et al., the Examiner asserts that it would have been obvious to one of ordinary skill in the art employ toremifene and its analogs such as idoxifene or droloxifene for the treatment of angitis (small vessel disease).

Ito et al. provide no motivation to employ toremifene or any analog thereof to treat any disorder other than one associated with autoreactive T cells.

Yang discloses methods to identify agents for the treatment of osteoporosis or serum lipid lowering. The method includes the use of eukaryotic cells having a promoter region of a TGF-beta gene that is a raloxifene responsive element (column 7, lines 16-32). The method identifies agents that induce expression from a raloxifene responsive element without inducing deleterious side effects associated with current anti-osteoporosis therapy regimes (abstract). The results in Table 1 show that estradiol, raloxifene and tamoxifen induced expression from TGF-beta2 and TGF-beta3 derived promoters, not TGF-beta1 derived promoters, that were present in human osteosarcoma cells (MG63 cells). The remaining agents were screened on cells with TGF-beta3 derived promoters, i.e., MG63 cells, CHO (Chinese hamster ovary) cells or MCF-7 (breast cancer) cells.

The screening assay disclosed in Yang does not provide a reasonable expectation that an agent that elevates TGF-beta1 levels or a cytostatic dose of a compound of formula (I), would be useful to treat any disease, such as a cardiovascular or vascular indication characterized by a decreased lumen diameter.

Therefore, withdrawal of the § 103 rejections is respectfully requested.

CONCLUSION

Applicant respectfully submits that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney at (612) 373-6959 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being filed using the USPTO's electronic filing system EFS-Web, and is addressed to: Mail Stop Amendment, Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on this 27 day of November 2007.

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